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THE ADDICTION LIABILITY OF SYNTHETIC SUBSTITUTES FOR CODEINE

(Project Description)

Request to the Office of Naval Research for Renewal of

Contract NR 101-149
(NAonr-17-58).

1. Background Information.

Since 1951 the National Institute of Mental Health Addiction Research Center, U. S. Public Health Service Hospital, Lexington, Ky., has been carrying on a project designed to develop a synthetic substitute for codeine which would be as safe as codeine and as effective with respect to toxicity, antitussive activity, constipative activity, and addiction liability. The project has been financed in large part by funds from the Office of Naval Research, and this description constitutes a request for renewal of the project for the period 1 July 1959 to 30 June 1960.

The project was initiated because synthetic substitutes for codeine were badly needed since opium or morphine derived from opium constitute the only sources of codeine. Codeine is the most widely used narcotic drug in both civilian and military medical practice. The United States consumes 16 to 20 tons of this drug yearly so that, unless adequate synthetic substitutes are found, the nation must continue to stockpile opium or morphine

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in order to provide adequate supplies for both the civilian and military population in the event of war. The facilities of the NIMH Addiction Research Center are not sufficient to carry out this work in addition to the evaluation of potent new analgesics submitted by the Committee on Drug Addiction and Narcotics, National Research Council, unless additional funds are supplied through the Department of Defense.

2. Work Accomplished to Date.

Previous work has been summarized in annual progress reports forwarded to Capt. F. H. Quimby and Capt. T. K. Ruebush, Head, Physiology Branch, Office of Naval Research. More than 51 drugs have been screened as potential substitutes for codeine. Two very promising substitutes for suppression of cough, dextromethorphan and narcotine, have been discovered and both are on the market. Neither drug is addictive and both are effective and safe cough suppressants. Narcotine, unfortunately, is not a synthetic drug but a by-product of opium processing. However, continuing reports to the Committee on Drug Addiction and Narcotics, NRC, and clinical reports in the medical literature indicate that both drugs are effective cough suppressants. The antitussive phase of the problem is therefore, in a sense, no longer so urgent.

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There are however no compounds available which are known to be as effective and as safe as codeine for the relief of mild grades of pain. The outstanding substances so far uncovered in the program are dl- and d-Alpha-4-dimethylamino-1,2-diphenyl-3-methyl-4-propionoxybutane (dl- or d-propoxyphene, "Darvon"). Addictiveness of these drugs is so low that the Committee on Drug Addiction and Narcotics has ruled that they need not be subjected to the controls imposed by the Harrison Narcotic Act. Preliminary clinical data indicated that these drugs were nearly as effective as codeine in relieving pain. Unfortunately more recent information is not nearly so favorable, and we are now uncertain as to whether propoxyphene will be an adequate substitute for codeine for pain relief. Sufficient clinical data are still not available to assess toxicity of the compounds in ordinary clinical practice.

During the past year 3-Methyl-N-desmethylmorphine (norcodeine) and d-methadone were shown to be less addictive than codeine. Clinical trial of both substances has been recommended. 1-(3-Diphenyl-3-carbonitril-propyl)-4-phenyl-4-carbethoxypiperidine (R-1132), which has been shown to be extremely effective as a constipative agent and which may be capable of replacing codeine or morphine for this purpose, was studied during the year. This compound, though addictive is

less so than codeine. Two promising potent analgesics, 3-Hydroxy-N-phenethyl benzmorphan (NIH-7519), and 3-Hydroxy-N-phenacylmorphinan (NIH-7525), were partly investigated. Although both drugs are many times as potent as morphine, abstinence was quite mild after withdrawal following direct addiction experiments. A study of the 3-methyl analogues of these drugs would be of considerable interest.

3. Need for Continuation of the Project.

At present, the chief justification for continuation of the project is the urgent need for a substitute for relief of mild grades of pain. As pointed out above, propoxyphene no longer seems to be as promising as was originally hoped. At the moment no completely satisfactory substitute for codeine for pain relief has been found. For this reason it is essential to continue the search.

4. Work Proposed.

During the period from 1 July 1959 to 1 July 1960 we propose to test the clinical pharmacology and addictive properties of 3-Methoxy-N-phenethyl-benzmorphan (the methyl analogue of NIH-7519), and of 3-Methoxy-N-phenacylmorphinan (the methyl analogue of NIH-7525). We also will undertake studies of l-3-Hydroxy-N-gamma gamma-dimethylallylmorphinan, a weak morphine antagonist that possesses analgesic properties, and

of the butyl ester analogue of R-1132. We also hope to initiate studies on a new group of synthetic analgesics -- the benzimidazoles. In addition, studies of other substances regarded as potential codeine substitutes by the Committee on Drug Addiction and Narcotics will be carried out, as advised by that body.

5. Methods.

The methods used are the standard addiction liability testing methods of the NIMH Addiction Research Center. These tests are accepted as legal standards by the Committee on Drug Addiction and Narcotics and have been described in previous project descriptions, which should be consulted for details.

6. Evaluation of Data.

Evaluation of data has been covered in previous project descriptions.

7. Location of the Project.

Work will be carried out in the NIMH Addiction Research Center, PHS Hospital, Lexington, Ky. This institution provides the two necessary facilities for the type of work to be undertaken: (1) pool of patients who will volunteer for experiments with drugs, and (2) strict environmental control, which prevents introduction of drugs other than those under study into the experimental situation.

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8. Experimental Personnel.

Work will be carried out under the direction of Harris Isbell, M.D., Director, NIMH Addiction Research Center. This investigator has had fifteen years of experience in research on narcotic drug addiction and has an extensive bibliography in the field. He will be assisted by two other experienced physicians, Dr. H. F. Fraser and Dr. Abraham Wikler, both of whom have had extensive research in this type of work, and many publications. The part-time services of a biochemist, neuropharmacologist, and research psychologist are also available. A special ward for the conduct of these studies has been made available by the hospital and is currently in operation.

9. Estimated Cost.

The estimated costs are shown on the attached sheet. The amount of money requested is identical to that requested for the last year (fiscal 1959) and amounts to [redacted]. The personal services budget reflects some changes that have been made among the personnel working on the project.

Harris Isbell, M.D.
Director

Attachment

31 January 1959

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1. Personal Services

   4 Psychiatric Aides (GS-6, [redacted])

   1 Psychologist (GS-5)

   1 Animal Caretaker (GS-3)

   1 Clerk-Stenographer (GS-4)

   Premium Pay (night differential, holiday pay, etc.

   Civil Service Retirement

   Total Personal Services

2. Travel

3. Miscellaneous (supplies, equipment, etc.)

   TOTAL

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